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EFFECTS OF IRON PARTICLES ON BEHAVIOR AND BRAIN FUNCTION: INITIAL STUDIES

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INTRODUCTION

Successful operations in space depend in part on the performance capabilities of astronauts and little is known about potential consequences of exposure to ionizing radiation on behavior and the brain during manned space flights. This possible threat has not been given much attention, since all manned mission have been located in low equitorial orbit and radiation there has not been considered hazardous. Future missions in space will probably involve polar orbits, long-term space travel beyond the Earth, and extended periods during which astronauts are operating outside their space craft. Since exposure to radiation increases under these conditions because of the absence of the Earth's normally protective transpolar magnetosphere, astronauts may be placed at considerable additional risk. An understanding of this risk may be vital to the survival and effective performance of future missions in space. Therefore, it is desirable to understand the medical and operational risks to personnel, including an assessment of possible behavioral and neurobiological deficits.

Radiation hazards outside the protection of the Earth's magnetic shield arise from solar flares and intragalactic cosmic rays. Intragalactic cosmic rays are composed of protons, alpha particles, and particles with high charge and

energy (HZE), such as iron. Although the hazards of exposure to cosmic rays are often minimized, they can destroy existing cells. Unless their effects can somehow be reduced, the effects on the various organs of the body, including the brain, by their continuous bombardment by radiation during long space flights could be disastrous. In some instances, it has been suggested that the effects of cosmic rays on space travelers could result in symptomatology resembling those of Alzheimer's or Parkinson's disease or advancing age, including significant cognitive and/or motor impairments. Such impairments could jeopardize the successful completion of a mission and have long-term consequences on the health of astronauts. Presently, little research has been done to address these issues.

Considerable advances have been over the last 20 years in the study of behavior and their neurobiological correlates. Specific paradigms are being used to investigate the effects of ionizing radiation on behavior (Mickley et al., 1988), as well as neurochemical and neurophysiological endpoints that underlie behavior under study. By combining these analyses with very sensitive behavioral assessments that can measure specific aspects of cognitive or motor performance following HZE irradiation, more information can be obtained concerning important biochemical and behavioral relationships that will eventually aid in predicting and controlling possible performance deficits occurring during manned space flight.

AFRRI RESEARCH IN SPACE BEHAVIORAL NEURORADIOBIOLOGY

General Considerations and Design

In order to gain some insight into the possible behavioral and neurological risks of irradiation in space, investigators at the AFRRI initiated a broad research effort using a variety of approaches. More specifically, the general research program is designed to gain information on possible alterations in behavior and the brain after exposure to heavy particles, such as those that might be encountered during space travel. The objectives are to describe and characterize radiation-induced behavioral deficits, determine their underlying causes, and develop approaches to minimize such deficits.

In May, 1987, the research group spent 3 weeks at the Lawrence Berkeley Laboratory (LBL) in Berkeley, CA, assessing the effects of 600 MeV

^{56}Fe particles delivered by their Bevalac after doses of 50, 100, or 500 rads on several behavioral and neurochemical endpoints (Table 1). These measurements were performed at various times after irradiation (Table 2) in an effort to obtain preliminary information on the potential hazards of space travel outside the protective shield of the Earth's magnetosphere. The effects of the three different doses of radiation were studied in rats at five different times after irradiation (3 days to 6 months). Although all of the data have not been fully analyzed (6-month groups), several important observations were made. Presented here are the results of studies examining the induction of a conditioned taste aversion by ^{56}Fe particles and the actions of these particles on sodium channels in synaptosomal membranes. Motor responses of animals exposed to ^{56}Fe particles and the mechanisms in the brain underlying them can be found in the paper of Joseph et al. (1988) in this volume.

In the basic experimental design of these experiments, several assumptions were made. First of all, in spite of the complexities of the radiation environment in space, it is presumed that conditions in space can be simulated on Earth under controlled conditions. Biological experiments in space are very expensive, yield too little information when sensitive systems have not yet been identified, and are generally impractical. Secondly, since little is known about what space radiation might do to behavior and the brain, effects found with other qualities of radiation are presumed likely to be found after exposures to space radiation. This approach provides a starting point for the design of appropriate experiments. Finally, since long-term, low-level irradiations are impractical with the sources available, the effect of a single dose over time is assumed to provide useful insights into how space radiation might affect the behavior and the brain. This assumption may be especially useful when studying the brain, since the brain does not significantly repair itself after damage.

The irradiations were performed at the Lawrence Berkeley Laboratory (LBL) with the remainder of the experiments completed at the AFRRI. Male Sprague-Dawley rats were irradiated by 600 MeV ^{56}Fe particles delivered by the LBL Bevalac. Iron particles were chosen because of their high LET and the difficulty to shield against them. Doses of 50, 100, and 500 rads were used to reflect the maximum exposures expected. Measurements were made at five time intervals after irradiation ranging from 3 days to 6 months in order to look for acute and delayed effects.

TABLE 1

EXPERIMENTAL MEASURES

BEHAVIORAL ENDPOINTS	
Taste Aversion Learning	(Index of Nausea & Emesis)
Motor Tasks:	
Inclined Screen	(Muscle Tone & Stamina)
Wide Rod	(Motor Coordination)
Narrow Rod	(Motor Coordination)
Wire Suspension	(Upper Body Strength)
NEUROCHEMICAL ENDPOINTS	
Sodium Channels	(Basic Neuronal Process)
Dopamine Release	(Motor Function)
Catecholamines and Turnover	(Brain Damage & Rate of Information Transfer)

TABLE 2

GENERAL EXPERIMENTAL DESIGN
FOR MAY 1987 EXPERIMENTS

ANIMAL MODEL

Male Sprague-Dawley Rats

RADIATION SOURCE

600 MeV/nucleon Iron Particles (LBL Bevalac)

DOSES

50, 100, 500 Rads

DOSE RATE

100 Rads/min

TIMES AFTER IRRADIATION

3 Days, 8 Days, 14 Days, & 6 Months

General Methods

Five behavioral and three neurochemical endpoints were assessed in these experiments (Table 1). These endpoints were chosen because of their sensitivity to other qualities of radiation. The behavioral endpoints include the conditioned taste aversion (CTA), an index of nausea and vomiting, and several motor tasks, measures of muscle tone, stamina, coordination, and upper body strength. The neurochemical endpoints include the movement of sodium ions through channels, a basic neuronal process; dopamine release, a regulator of motor activity; and catecholamine levels and turnover, a rough estimate of brain damage and the rate of information transfer in the brain.

Male Sprague-Dawley Crl:CD(SD)BR rats (Charles River Breeding Laboratories, Kingston, NY) weighing 200-300 g were used in these experiments. Rats were quarantined on arrival and screened for evidence of disease by serology and histopathology before being released from quarantine. The rats were housed individually in polycarbonate isolator cages (Lab Products, Maywood, NJ) on autoclaved hardwood contact bedding ('Beta Chip' Northeastern Products Corp., Warrensburg, NY) and were provided commercial rodent chow ('Wayne Rodent Blok' Continental Grain Co., Chicago IL) and acidified water (pH 2.5 using HCl) ad libitum. Animal holding rooms were kept at 21 $\pm$ 1° C with 50 $\pm$ 10% relative humidity on a 12-hr light:dark lighting cycle with no twilight.

The rats were irradiated with high-energy ^{56}Fe particles (600 MeV) in the Bevalac at the LBL. The animals were irradiated in well-ventilated Plexiglas holders with one of three doses, including 50, 100, and 500 rads, at a dose-rate of 40-140 rad/min. Dosimetric support was provided by personnel at the Bevalac. Animals irradiated with other radiation sources were exposed to a single dose of 50, 100, or 500 rads of gamma photons from a ^{60}Co source at a rate of 40 rads/min or high-energy electrons (18.6 MeV) from a linear accelerator. Radiation dosimetry was performed using paired 50-ml ion chambers. Delivered dose was expressed as a ratio of the dose measured in a tissue-equivalent plastic phantom enclosed in a restraining tube, to that measured free in air.

General Observations after ^{56}Fe Irradiation

Although not a specific part of the experimental design, any unusual

reactions by the animals were noted. Based on subjective observations, the animals appeared normal after irradiation with ^{56}Fe particles. However, after exposure to 500 rads, several changes were observed. The exposed rats progressively lost weight, totaling about 20% of body weight over a 14-day period. In addition, they experienced a reduction in muscle tone, a hind limb tremor, and hypothermia (animals cool to the touch) 3 days after irradiation, effects that had disappeared by 8 days after irradiation.

CONDITIONED TASTE AVERSION LEARNING AFTER IRRADIATION

Characteristics of the Conditioned Taste Aversion

Animals have developed over the course of evolution mechanisms to help prevent accidental poisoning, the best-known one being the emetic response. Emesis can occur as a result of consuming presumably tainted food that is then expelled from the stomach. In addition to emesis, animals are also capable of avoiding potentially toxic substances after a single ingestion of quantities less toxic than those required to induce vomiting. This is done through a process called the conditioned taste aversion (CTA). A CTA develops when the animal associates the taste of novel tasting food with a physiological response, possibly illness, and then subsequently avoids further ingestion of that food. In a laboratory setting, a CTA is typically induced by pairing a normally preferred but novel tasting fluid with exposure to a toxin. The animal will then avoid drinking the fluid when presented again.

The conditioned taste aversion (CTA) paradigm in the rat can be used as a model system to study the mechanisms by which exposure to non-lethal levels of ionizing radiation can produce changes in the behavior of an organism (Rabin and Hunt, 1986). Because the functional effects of emesis and taste aversion learning are similar, in the sense that they limit the intake and/or absorption of toxic substances, a number of investigators have argued that the CTA paradigm represents a model system for the study of radiation-induced nausea and emesis (Garcia et al., 1985; Rabin and Hunt, 1986). Therefore, the CTA provides an index of the probability that nausea and emesis will occur.

The CTA paradigm offers a number of advantages over emesis models. The paradigm can be used with rats, inexpensive and easily used animals. They are small enough that more uniform fields of radiation can be obtained with particle accelerators than with larger animals. Because a CTA can be easily induced in a relative large number of animals, a great deal of information can be accumulated quickly as well as the characterization of any responses. Since the mechanisms underlying the CTA and emesis appear to be similar, this approach will allow for the formulation of more specific hypotheses that could be applied eventually to emesis models.

The CTA induced by ionizing radiation has been extensively studied and a clearer idea of how it develops has been emerging. The most important discovery is the involvement of a specific nucleus in the brain stem, the area postrema. The area postrema has been demonstrated to play an critical role in the development of CTAs induced by a broad range of unrelated toxins. This part of the brain is sufficiently important that if the area postrema is lesioned, the development of a CTA is blocked. These toxins include not only ionizing radiation (Ossenkopp, 1983; Rabin et al., 1983), but also lithium chloride (Ritter et al., 1980; Rabin et al., 1983), copper sulfate (Rabin et al., 1985), aluminum chloride (Rabin and Hunt, unpublished observation), paraquat (Dey et al., 1987), angiotensin II (Rabin et al., 1986), amphetamine (Rabin et al., 1987), WR-2721 (Rabin et al., 1986), and cisplatin (Rabin and Hunt, unpublished observation). In addition, other evidence indicates that the area postrema is also required for the development of emesis (Wang et al. 1958; Brizzee, 1970; Harding et al., 1985; Rabin et al., 1986). Not all toxic drugs induce CTAs through the area postrema. For example, ethanol- and morphine-induced CTAs are not blocked by lesions of the area postrema (Hunt et al., 1987; Rabin and Hunt, unpublished observation).

Since many unrelated toxins induce CTAs through the area postrema, it has been suggested that a common mechanism may underlie all these effects (Rabin and Hunt, 1986). Also, since toxins are generally foreign substances, specific receptors for each possible toxin are not likely to have evolved. Consequently, an intermediary mechanism in the induction of CTAs and emesis involving one or more secondary mediators has been postulated (Hunt et al., 1965; Rabin and Hunt, 1986). If these mediators interact with receptors in the area postrema, they may then activate the neural circuits that evoke CTAs.

Induction of a CTA after Exposure to ^{56}Fe Particles

Research was initiated to determine whether high-energy iron particles could induce a CTA similar to other qualities of ionizing radiation, such as gamma photons. The first experiments were designed to find the doses of ^{56}Fe particles that would induce a CTA and compare the sensitivity of the animals to those irradiated with gamma photons or high-energy electrons.

Conditioned taste aversions were produced by first placing the rats on a 23.5-hr water deprivation schedule for 5 days during which water was available for only 30 min daily during the early light phase of the diurnal cycle. On the conditioning day (day 6), the rats were presented with a solution of 10% sucrose, after which the intake of the fluid was recorded. Immediately following the drinking period, rats were irradiated with the doses stated above. On the following day (test day), 10% sucrose was presented again and the consumption during a 30-min period was recorded. A CTA existed when the amount of fluid consumed on the test day was significantly less than that consumed on the conditioning day.

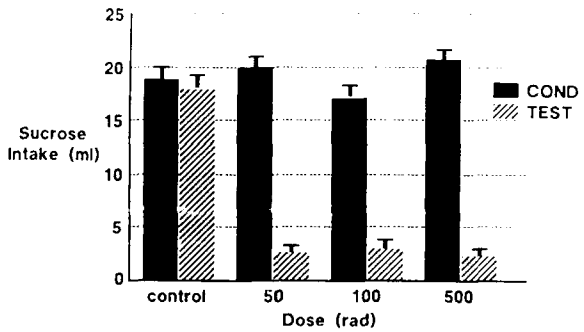

Fig. 1. Conditioned taste aversions after different doses of ^{56}Fe ions. Sucrose intake was significantly reduced after all doses studied. The maximum effect of the radiation is presumed to be < 50 rads.

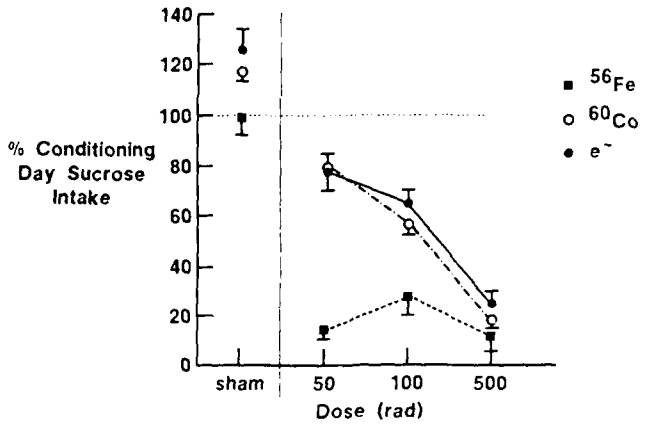

Fig. 2. Conditioned taste aversions after different doses of ^{56}Fe ions, gamma photons (^{60}Co), and high-energy electrons (LINAC). ^{56}Fe ions were at least 10 times more effective in inducing a CTA than do gamma photons or electrons.

Exposure to all doses of high-energy ^{56}Fe particles tested resulted in significant dose-dependent reductions in sucrose intake, indicating the development of a CTA. In fact, maximum reductions were found after all 3 doses of radiation (Fig. 1). For comparison, when rats were exposed to these same doses of gamma photons or high-energy electrons, dose-dependent decreases in sucrose intake were observed, indicating the development of a CTA (Fig. 2). However, ^{56}Fe particles were considerably more effective than the other two qualities of radiation. A maximal CTA was observed only after exposure to 500 rads of photons or electrons. A further characterization of the dose-response effects of ^{56}Fe particles compared to other qualities of radiation is currently in progress.

CEREBRAL SODIUM CHANNELS AFTER IRRADIATION

Characteristics of Sodium Channels in the Brain

The generation and propagation of electrical impulses or action potentials in neurons is initiated by the rapid inward flow of sodium ions across the

neuronal plasma membrane (Hodgkin and Huxley, 1952). In the resting state a neuron maintains a resting membrane potential that results from the unequal distribution of sodium, potassium, and chloride ions across the membrane (Koester, 1981a,b). When neurons are electrically excited, sodium ions flow inward on their concentration gradient until the membrane potential is reversed (Koester, 1981c). The movement of potassium ions out of the neuron proceeds until the neuron has repolarized and the neuron is again in the resting state.

Sodium ions enter the neuron through pores in the membrane called channels. These channels are specific to sodium and traverse the neuronal plasma membrane. They are glycoproteins containing multiple subunits (Catterall, 1982) and have an absolute requirement for lipids for normal functioning (Tamkin et al., 1984). At least three functional sites within sodium channels have been identified based on the actions of specific neurotoxins (Catterall, 1980). Site I, located on the external surface of the neuronal membrane, binds tetrodotoxin and saxitoxin, drugs that block the generation of action potentials. Site II, located in the lipid core of the membrane, binds batrachotoxin and veratridine, lipid-soluble drugs that activate sodium channels. And site III, located on the membrane surface but with projections down to site II, binds scorpion and sea anemone toxins that enhance the actions of toxins on site II but have no intrinsic activity of their own. Neurochemically, the functioning of the sodium channel can be studied with a synaptosomal (pinch-off nerve endings) preparation (Krueger and Blaustein, 1980; Tamkin and Catterall, 1981). The rate of uptake of ^{22}Na can be measured after exposure to the neurotoxins batrachotoxin or veratridine, thereby assessing what would occur under normal physiological conditions.

Sodium Channel Function after Exposure to ^{56}Fe Particles

The rate of ^{22}Na uptake was determined in synaptosomes from the cerebral cortex as detailed previously (Mullin et al., 1986). A crude mitochondrial preparation containing synaptosomes was prepared from a cortical homogenate. The final pellet was resuspended in ice-cold incubation buffer (8-10 ml/brain) containing 5.4 mM KCl, 0.8 mM $MgSO_4$, 5.5 mM glucose, 130 mM choline chloride, and 50 mM N-2-hydroxyethyl-piperazine-N'-2-ethanesulfonic acid (HEPES), with the pH adjusted to 7.4 with Tris base. The uptake of ^{22}Na was measured as follows. Aliquots (50 μl) of the synaptosomal suspension were incubated for 2 min at 36° C. The neurotoxin

veratridine was then added, and the incubation was continued for an additional 10 min. The samples were then diluted with 300 μl of uptake solution containing 5.4 mM KCl, 0.8 mM $MgSO_4$, 5.5 mM glucose, 128 mM choline chloride, 5 mM ouabain, 2 mM NaCl, 1.3 μCi ^{22}Na, 100 μM veratridine, and 50 mM HEPES (pH adjusted to 7.4 with Tris). After a 5-sec incubation, uptake was terminated by adding 3 ml of ice-cold wash solution containing 163 mM choline chloride, 0.8 mM $MgSO_4$, 1.7 mM $CaCl_2$, 1 mg/ml of bovine serum albumin, and 5 mM HEPES (pH adjusted to 7.4 with Tris). The mixture was rapidly filtered under vacuum through a cellulose filter with 0.45-μm pores, and the filters were washed twice with 3 ml of wash solution. Radioactivity was determined by liquid scintillation spectrophotometry. The data were expressed as specific uptake determined by subtracting nonspecific uptake (samples containing 1 μM tetrodotoxin) from total uptake.

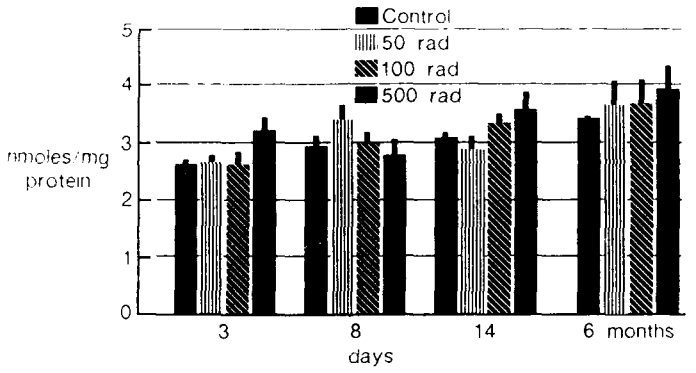

Fig. 3. ^{22}Na uptake after different doses of ^{56}Fe particles and different intervals after irradiation. No significant differences were observed under any of the experimental conditions studied.

Rats were irradiated with ^{56}Fe particles in the manner described above. Measurements of veratridine-stimulated sodium uptake in synaptosomes did not reveal any consistent and statistically significant changes after exposure of any of the four doses of radiation nor at any of the three intervals after irradiation (Fig. 3).

GENERAL DISCUSSION OF RESULTS

The experiments completed to date demonstrate that ^{56}Fe particles can induce a CTA that may represent a state of illness, possibly nausea. These results along with those presented by Joseph et al. (1988) suggest that the behavioral effects of exposure to ^{56}Fe particles may be at least 10 times greater than those observed following exposure to gamma photons or high-energy electrons. They also may reflect a greater chance for the occurrence of nausea and emesis in astronauts exposed to a space radiation environment during longer term missions.

The successful completion of missions in space depends in part on behavioral and neural integrity of the astronauts. Given the potential significance of the data presented, it is important to seriously pursue an active program of research into the possible behavioral and neural deficits that might occur in space as a result of exposure to radiation. By combining sensitive behavioral assessments that can measure cognitive or motor performance with neurochemical analyses following HZE irradiation (e.g. Joseph et al., 1988), more information can be obtained concerning important behavioral and biological relationships that will aid in predicting and controlling possible performance deficits during manned space flight.

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